for new claims 29-31 can be found at least at page 12, lines 9-10. Accordingly, claims 1-31 are currently under consideration.

For the Examiner's convenience, an attachment listing the claims presently under consideration, incorporating the current amendments, is attached to this response.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded claimed subject matter or embodiments in one or more future continuation and/or divisional applications.

Applicants acknowledge the Examiner's indication of allowability of claims 10 and 22 if rewritten in independent form.

Concerning the drawings

Applicants acknowledge that formal drawings will be required when the application is allowed.

Objection of claim 18 based on informalities

The Examiner has objected to claim 18 based on the presence of "a a" in the claim. Applicants have amended claim 18 to delete one "a" thereby mooting the Examiner's objection.

Obviousness-type double patenting rejection

Claims 1-28 stand provisionally rejected, under the judicially-created doctrine of obviousness-type double patenting, over claims 1-32 of U.S. Patent No. 5,871,726.

Applicants traverse this rejection.

Applicants submit that the present claims are patentably distinct from U. S. Patent No. 5,871,726. The present claims recite a cell status-specific TRE. At page 12, lines 18-22, the present specification discloses that cell status-specific TRE is clearly distinguished from a cell type or tissue specific TRE, which relates to a differentiation state of a cell, such as is disclosed in U. S. Patent No. 5,871,726. A tissue-specific TRE is one which functions specifically in cells of a specific differentiation state, such as prostate tissue, liver tissue, breast tissue, melanoma etc.

In U.S. Patent No. 5,871,726, the tissue specific TRE is specific for prostate specific antigen. Therefore, the cell status-specific TREs of the present claims are clearly distinguished from the tissue specific TREs disclosed in U.S. Patent No. 5,871,726.

The present claims are not drawn to the same methods as claimed in U.S. Patent No. 5,871,726 and the claims in U.S. Patent No. 5,871,726 do not represent a species of the present claims.

Therefore, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection.

35 U.S.C. § 112, first paragraph rejection of claims 27-28

Claims 27-28 are rejected under 35 U.S.C.112, first paragraph, because the specification, while allegedly enabling for a method of conferring selective cytotoxicity with direct administration of adenovirus or suppressing tumor growth with direct administration of adenovirus comprising E1A under transcriptional control of a hypoxia responsive element and a PSA-TRE, "does not reasonably provide enablement for any and all cell status-specific TRE in an adenovirus delivery system in any and all types of cells by any and all methods of administration". See Office Action, page 4. The Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants respectfully traverse this rejection.

As an initial matter, Applicants would like to respectfully clarify a possible misunderstanding held by the Examiner regarding the invention. At page 5, lines 1-4, the Examiner refers to the claims as being directed to "gene therapy delivery by a method of adenovirus administration". Claim 27 recites a method for conferring selective cytotoxicity comprising contacting a cell which allows a cell status-specific TRE to function with a replication competent adenovirus vector with an adenovirus gene essential for replication under transcriptional control of a cell status-specific TRE. Claim 28 recites a method for suppressing tumor growth comprising introducing a replication competent adenovirus vector comprising an

adenovirus gene essential for replication under transcriptional control of a cell status-specific TRE into a tumor cell which allows a cell status-specific TRE to function. Neither claim 27 nor claim 28 recite a method for gene delivery, that is, delivery of a heterologous gene into a cell for its expression to achieve therapeutic purposes, which is the standard definition of gene therapy. The Examiner also repeatedly refers to levels (and duration) of gene expression, therapeutic genes and gene therapy art. The goal of claimed invention is to selectively disable or kill a target cell *via* adenovirus replication. These effects are selective, that is targeted to a desired cell, by the choice of cell-status TRE. The Examiner's reference to "gene therapy" standards in making the Section 112, first paragraph rejection of claims 27-28, is inappropriate.

In rejecting claims 27-28, the Examiner relies on Orkin et al., and alleges that "the importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy" and that expression levels have not been demonstrated with regard to rendering treatment to a model for cancer. The Examiner's inappropriate reliance on gene therapy as a basis for this rejection has been discussed above.

The Examiner further alleges at page 6 of the Office Action that:

> Diseases and/or disorders such as tumor require that the therapeutic gene be targeted to specific cells and/or tissues in order to achieve a therapeutic result. The specification fails to teach any specific parameters or conditions under which cell targeting can be predictably achieved.

The Examiner also alleges at the last sentence of page 6 that the specification provides no teachings on parameters for which vectors can be targeted to which cells. Applicants strongly disagree with these statements. Firstly, as stated earlier, the invention of claims 27 and 28 results in selective cytotoxicity or suppression of tumor growth of desired cells which is distinguished from "gene therapy" or targeting of a "therapeutic gene" to the cells. Furthermore, a review of the specification will reveal that cell targeting is achieved by virtue of the TRE employed. As claim 27 recites, contacting a target cell which allows a cell status-specific TRE to function with an adenovirus vector comprising the cell status-specific TRE provides for targeting of the

adenovirus vector to the cell in the sense that adenovirus preferentially replicates in those cells. Similarly, as recited in claim 28, introducing an adenovirus vector comprising a cell status-specific TRE into a tumor cell that allows the cell status specific TRE to function provides for targeting of the adenovirus vector to the tumor cell. The use of the cell status-specific TRE allows for targeting to a desired cell that allows the TRE to function.

The Examiner further alleges that cell targeting methodologies have not reached clinical application. The law makes it clear that Section 112, first paragraph does not require a showing of clinical results.

The Examiner alleges that a clear correlation to achieving *therapeutic expression* must be provided by the specification. As stated earlier, the methods of claims 27 and 28 result in selective cytotoxicity (claim 27) or tumor suppression (claim 28). No correlation to achieving therapeutic *expression* of genes is required because the claims do not recite delivery of therapeutic genes to target cells.

The Examiner alleges that Eck & Wilson support the importance of tailoring a gene therapy vector and method to specific diseases. The Examiner's inappropriate reliance on gene therapy has been discussed above. "Tailoring" or optimizing a method for a specific disease would not require undue experimentation for the skilled artisan. Further, "tailoring" has been achieved by the invention in the sense of providing for selective adenoviral replication in cells which allow a cell status-specific TRE to function.

In accordance with requirements for enablement, the specification teaches how to make and use the adenovirus vectors of the invention. Pages 21- 48 (see pages 46-48); Example 1.

In view of the arguments presented above, Applicants respectfully request withdrawal of this rejection.

35 U.S.C. §112, second paragraph rejection of claim 1

Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended claim 1 to recite that the TRE is a cell status-specific TRE, thereby obviating the Examiner's rejection. Applicants have added claims 29-31 that recite that the cell status-specific TRE is a promoter or an enhancer or both a promoter and enhancer.

Applicants respectfully request withdrawal of this rejection.

35 U.S.C. §102(e) rejections

A. Claims 1-3, 5-8, 11, 14, 18-20 and 23-28 stand rejected as allegedly anticipated by Hallenbeck et al. (U.S. Patent No. 5,998,205).

Applicants respectfully traverse this rejection.

In order for a reference to anticipate a claim, the reference must contain all the elements of the claim. The rejected claims recite a "cell status-specific" TRE which functions in a cell which exhibits a particular physiological condition which condition is reversible and/or progressive. The Examiner acknowledges this property. Office Action at page 5, second full paragraph. At page 12, lines 18-22, the specification discloses that cell status-specific TRE is distinguished from a cell type or tissue specific TRE, which relates to a differentiation state of a cell, such as is disclosed in Hallenbeck et al. The claims also show this distinction by separately reciting "cell status-specific" TREs and "cell type-specific" TREs (see, for example, claim 18).

Hallenbeck et al. disclose at the paragraph bridging column 8 and column 9, that the tissue-specific transcriptional regulatory sequence is one which functions specifically in cells of a specific differentiation state, such as liver tissue, breast tissue, melanoma etc. The Examiner herself acknowledges this in stating that Hallenbeck et al. disclose and teach tissue-specific adenovirus vectors. Office Action at page 11. Hallenbeck does not disclose cell status-specific TREs in its adenoviral vectors. The tissue-specific TREs of Hallenbeck are clearly distinguished from the cell status-specific TREs of the claims. Therefore, each and every element of the claimed invention is not in Hallenbeck et al. and the Section 102(e) rejection must fail as a matter of law.

B. Claims 1-8, 11, 14-20 and 23-27 stand rejected as allegedly anticipated by Henderson et al. (U.S. Patent No. 5,871,726).

Applicants respectfully traverse this rejection.

In order for a reference to anticipate a claim, the reference must contain all the elements of the claim. As discussed above, the rejected claims recite a "cell status-specific" TRE, which functions in a cell that exhibits a particular physiological condition, which condition is reversible and/or progressive. Henderson et al. describe tissue or cell-type specific TREs and do not disclose cell status specific TREs. Therefore, Henderson et al. do not recite each and every element of the claimed invention and therefore cannot anticipate the claimed invention.

C. Claims 1 and 9 stand rejected as allegedly being anticipated by Webster et al. (U.S. Patent No. 5,834,306).

Applicants respectfully traverse this rejection.

In order for a reference to anticipate a claim, the reference must contain all the elements of the claim. Each and every element of the claimed invention, that is a replication-competent adenovirus vector comprising an adenovirus gene essential for replication under transcriptional control of a cell status-specific TRE, is not disclosed in Webster et al. As the Examiner states, Webster et al. disclose methods and compositions relating to chimeric genes containing i) a tissue-specific promoter and ii) a hypoxia response enhancer element, both of which are operably linked to a selected heterologous gene.

Therefore, Webster et al. do not anticipate the claimed invention.

Applicants respectfully request withdrawal of all rejections under 35 U.S.C. 102(e).

35 U.S.C. § 103(a) rejection of claims 1-28

Claims 1-28 stand rejected as allegedly unpatentable over Hallenbeck et al. (U.S. Patent No. 5,998,205) taken with Webster et al. (U.S. Patent No. 5,834,306) and Henderson et al. (U.S. Patent No. 5,871,726).

Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings.

Applicants submit that the combination of references cited does not provide motivation for arriving at the claimed invention, and, even if combined, the combination of references does not produce the claimed invention.

As an initial matter for clarification, the Examiner framed this rejection in terms of (in effect) characterizing the rejected claims as adenovirus vectors comprising a hypoxia element (HRE) and a cell type specific element (PSA). Office Action, page 16 ("Hallenbeck differs from the claims in that the reference fails to disclose insertion of hypoxia responsive element as the cell status-specific TRE and wherein the cell status-specific TRE comprises an HRE and the cell-type specific TRE is a PSA-TRE of the instant invention."). However, the Office Action states that all pending claims (1-28) are rejected as allegedly obvious. Therefore, Applicants will address the obviousness rejection as though levied against those claims. Applicants note that claims 1 (as amended) recites that the adenovirus vector of the invention is replication competent and has a gene essential for replication under transcriptional control of a cell status specific TRE.

Hallenbeck et al. relate to the use of tissue-specific transcriptional regulatory elements (TRE) in adenoviral vectors and have no teaching, suggestion or appreciation of the use of cell status TREs in order to target to cells in a particular physiological state that is reversible and/or progressive.

Neither Henderson et al. nor Webster et al. cure the deficiencies of Hallenbeck et al. Nor can Webster et al. be properly combined with Hallenbeck et al. or Henderson et al.

Henderson et al. relate to tissue-specific transcriptional regulatory element, and have no teaching or suggestion of cell status-specific TREs. Webster et al. have no teaching or suggestion of a replication-competent adenovirus vector comprising an adenoviral gene essential for replication under transcriptional control of a cell-status TRE. The chimeric DNA in Webster et al. requires three specific elements, a selected heterologous (i.e., non-adenoviral) gene, a tissue specific promoter and a hypoxia enhancer. Webster et al. suggest that the desired results can be achieved with the particular combination of the recited three elements. Thus, even if the references could be combined, a point which Applicants do not concede, this combination could

not and would not result in a mere substitution of a hypoxia TRE for a tissue specific TRE. The configuration taught in Webster et al. precludes such a combination.

Furthermore, Applicants submit as Exhibit A, attached hereto, the International Preliminary Examination Report (IPER) as prepared by the U.S. receiving office of the PCT. The IPER indicates that another U.S. examiner has concluded that claims 1-28 of the PCT application, identical to claims 1-28 reviewed by the present Examiner, were found to be novel and have inventive step.

Applicants respectfully point out an apparent inconsistency in the Examiner's position with respect to claims 27 and 28. On one hand, these claims have been rejected as allegedly non-enabled, based on alleged unpredictability and uncertainty of the art. (However, as discussed above, Applicants assert that the Examiner has erroneously applied "gene therapy" basis for this rejection.) On the other hand, the Examiner has rejected these same claims as allegedly obvious, despite the legal requirement for a *prima facie* case of obviousness that there must be a reasonable expectation of success in view of the cited references.

Therefore, in view of the arguments and facts presented above, Applicants respectfully request a withdrawal of the rejection.

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952** referencing docket no. 348022001200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: December 6, 2000 By: _____

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